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Gastric cancer

Risk of endocrine pancreatic insufficiency in patients receiving adjuvant chemoradiation for resected gastric cancer ☆

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ABSTRACT

Background: Adjuvant radiotherapy combined with 5-fluorouracil based chemotherapy has become the new standard after curative resection in high risk gastric cancer. Beside many complications due to surgery, the addition of chemotherapy and radiotherapy as adjuvant treatment may lead to both acute and late toxicities. Pancreatic tissue irradiation during this adjuvant treatment because of incidental and unavoidable inclusion of the organ within the radiation field may affect exocrine and endocrine functions of the organ.

Materials and methods: Fifty-three patients with gastric adenocarcinoma were evaluated for adjuvant chemoradiotherapy after surgery. While 37 out of 53 patients were treated postoperatively due to either serosal or adjacent organ or lymph node involvement, 16 patients without these risk factors were followed up regularly without any additional treatment and they served as the control group. Fasting blood glucose (FBG), hemoglobin A1c (HBA1c), insulin and C-peptide levels were measured in the control and study groups after the surgery and 6 months and 1 year later.

Results: At the baseline there was no difference in FBG, HbA1c, C-peptide and insulin levels between the control and the study groups. At the end of the study there was a statistically significant decline in insulin and C-peptide levels in the study group, (7.5 ± 6.0 vs 4.5 ± 4.4 IU/L, p: 0.002 and 2.3 ± 0.9 vs 1.56 ± 0.9 ng/ml, p: 0.001) respectively.

Conclusions: Adjuvant radiotherapy in gastric cancer leads to a decrease in beta cell function and insulin secretion capacity of the pancreas with possible diabetes risk. Radiation-induced pancreatic injury and late effects of radiation on normal pancreatic tissue are unknown, but pancreas is more sensitive to radiation than known. This organ should be studied extensively in order to determine the tolerance doses and it should be contoured during abdominal radiotherapy planning as an organ at risk.

Radiation therapy is unavoidably associated with early and late side effects and the normal tissue toxicity is the major obstacle to effective radiation dose administration. Acute and especially late side effects are the major concern in treated patients.

There is an increased use of radiotherapy with concomitant chemotherapy after surgery in the management of gastric cancer [1]. The possibility of encountering late radiation-related side effects increases with increase in survival of these patients.

The tolerance of the spinal cord, kidneys, liver, small bowel, stomach to radiation has been well defined and incorporated into radiation plan evaluations. In contrast, the potential early and late side effects of radiotherapy on normal pancreatic tissue are not well defined. The exact dose of radiation that causes 5% of the patients to have radiation induced pancreatic complications within 5 years is unknown and no late toxicity related to pancreatic tissue exposure to radiation has been mentioned in major textbooks of radiotherapy. Pancreas is not cited among the organs at risk, either in the Emami late tissue toxicity report or in quantitative analyses of normal tissue effects in the clinic (QUANTEC) report [2,3]. The pancreas lies inferior to the stomach and it is situated within the field of radiation with inevitable exposure to irradiation during adjuvant treatment of gastric cancer.

Pancreas has both exocrine and endocrine functions. Acinar cells belong to the exocrine pancreas, and constitute more than 90% of the organ. They secrete digestive enzymes. Islets of Langerhans are responsible for the endocrine function of the organ [4]. Loss of exocrine function of the pancreas causes malabsorption and loss of endocrine function of the pancreas leads to diabetes mellitus (DM).

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Glucose and glycosylated hemoglobin (HbA1c) levels are necessary for the diagnosis of diabetes. Plasma insulin and C-peptide levels can give information about the function of beta cells. C-peptide is used to monitor insulin production and its measurement determines endogenous insulin production capability of the beta cells.

In some animal studies, researchers have investigated morphologic and functional response of the irradiated pancreatic tissue [5,6]. Unfortunately these studies do not give us information about delayed effects of irradiation on the organ. One important observation regarding pancreatic radiation toxicity is the higher incidence of diabetes mellitus in survivors of childhood cancers who had undergone abdominal radiotherapy [7–9].

Pancreas as an organ at risk for radiation related late toxicity is not studied extensively and the underlying mechanism of the damage is not known.

This study is primarily designed for the evaluation of late radiation induced endocrine functional disturbance of the pancreatic tissue after being exposed to irradiation during adjuvant treatment of patients with operated gastric cancer.

Materials and methods

Patients with histologically proven nonmetastatic gastric adenocarcinoma who had curative surgical resection were evaluated for adjuvant treatment and were included in the study. Pathological staging was done according to the staging criteria of the American Joint Commission on Cancer [10]. Patients presenting with serosal (pT3), and or adjacent visceral organ (pT4) invasion, or with involved regional lymph nodes were considered suitable for adjuvant treatment. Thirty-seven patients were eligible for the adjuvant treatment and comprised the study group, while 16 patients (pT1, pT2 and N0) who did not receive adjuvant chemoradiotherapy comprised the control group. Patient characteristics comprising T, N stages, extent of lymph node dissection, surgical resection type were summarized in Table 1. No patients in the study group had T4 disease due to the direct involvement of pancreas, and none of the patients in the study group had undergone pancreatic tissue resection.

Adjuvant treatment plan was similar to the intergroup study presented in 2001 by MacDonald et al. [1]. Patients received bolus 5-fluorouracil and leucovorin; one cycle before, two cycles concomitant to and one cycle after radiation treatment. Radiation was delivered with either 6 or 15 MV photons by anterior and posterior parallel opposed fields to total dose of 46 Gy in 23 fractions with 2 Gy fractions per day, 5 days per week for 5 weeks. The radiation field included the tumor bed and the regional lymphatics according to the technique described by Smalley et al. [11]. Radiation planning was 2-dimensional as in MacDonald's study. All or most part of the pancreatic tissue was included in the radiation field due to 2-dimensional radiation planning and most of the pancreatic tissue has received the whole radiation dose calculated at midplane.

All patients gave informed consent. Blood samples were taken after operation and regularly at 3 or 6 month intervals and 1 year after surgery for the patients receiving no adjuvant treatment, and 1 year after the end of radiotherapy for patients receiving adjuvant treatment. One year time period was considered enough for late radiation toxicity evaluation.

Age, gender, height, weight and body mass index (BMI) were recorded. Fasting blood glucose, hemoglobin A1c, insulin and C-peptide levels were measured initially, at the 6th month and at the end of the study. All of the routine biochemical tests were carried out on Roche Diagnostics Modular Systems autoanalyser. Levels of insulin and C-peptide were measured by chemiluminometric immunoassay.

In addition to measurement of insulin and C-peptide levels, there are indirect methods for the assessment of insulin resistance and pancreatic beta cell function named as HOMA indices [12]. HOMA indices are formulated as follows:

HOMA-IR = [insulin × glucose]/22.5, which shows insulin resistance.
HOMA-Beta = [20 × insulin]/[glucose − 3.5], which shows insulin secretion capacity of the pancreas and beta cell function.

Both groups were similar according to, age, gender and BMI.
The study was approved by the local ethics committee.

Statistical analysis was performed with SPSS program. A p value less than 0.05 was considered statistically significant. Results were expressed as mean ± SD. Comparison between the groups were made with Student's t-test.

Results

Demographic features of the study and control group are summarized in Table 2. At baseline there was no difference in age, body weight, BMI, FBG, insulin, C-peptide, HbA1c levels between the control and the study group (Tables 2 and 3). Since radiation planning was 2-dimensional, no dose-volume histogram data are available for organs at risk including the pancreas.

In regard to FBG and HbA1c there was no difference between both groups at the 6th month and at the end of the study compared

Table 1
Patient characteristics comprising T, N stages, extent of lymph node dissection, and surgical resection type.

	Study group Radiotherapy (+)	Control group Radiotherapy (−)
T stage		
T1	–	4 (25%)
T2	10 (27%)	12 (75%)
T3	22 (59%)	–
T4	5 (14%)	–
N stage		
N0	5 (13.5%)	16 (100%)
N1	14 (38%)	–
N2	13 (35%)	–
N3	5 (13.5%)	–
Extent of lymph node dissection		
D0	3 (8%)	–
D1	26 (70%)	11 (68.7%)
D2	8 (22%)	5 (31.3%)
Surgical procedure		
Subtotal	20 (54%)	10 (62.5%)
Total	17 (46%)	6 (37.5%)

Table 2
Comparison of the study group (radiotherapy +) and the control group (radiotherapy −) according to age, gender, BMI, insulin, C-peptide and HbA1c at the beginning of the study.

	Study group Radiotherapy (+)	Control group Radiotherapy (−)	p
N	37	16	
Age (years)	52.92 ± 12.3	59.62 ± 11.3	N.S.*
Gender (F/M)	12/25	7/9	N.S.
BMI (kg/m^2)	23.06 ± 3.84	24.76 ± 4.74	N.S.
Insulin (U/L)	7.51 ± 6.0	8.25 ± 5.8	N.S.
C-peptide (ng/dl)	2.30 ± 1.0	2.65 ± 1.2	N.S.
HbA1c (%)	5.54 ± 0.5	5.89 ± 0.7	N.S.

* N.S.: non-significant.